Pathak, S., Main, B. G., Blencowe, N. S., Rees, J. R. E., Robertson, H. F., Abbadi, R. A. G., & Blazeby, J. M. (2020). A systematic review of Minimally Invasive Trans-Thoracic Liver Resection (MITTLR) to examine intervention description, governance and outcome reporting of an innovative technique. *Annals of Surgery*. https://doi.org/10.1097/SLA.0000000000003748

A systematic review of Minimally Invasive Trans-Thoracic Liver Resection (MITTLR) to examine intervention description, governance and outcome reporting of an innovative technique

Authors

Mr S Pathak[1,2,3]	Clinical Lecturer
Mr BG Main[1,2,3]	Clinical Lecturer
Ms NS Blencowe[1,2,3]	Clinical Lecturer
Mr JRE Rees[1,3]	Consultant Surgeon/ Senior Lecturer
Mr HF Robertson[1]	Medical Student
Mr R Abbadi[3]	Consultant Surgeon
Professor JM Blazeby[1,2,3]	Professor of Surgery

Affiliations

1. Bristol Center for Surgical Research, Population Health Sciences, Bristol medical School, Bristol, UK
2. NIHR Bristol Biomedical Research Center
3. University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Corresponding Author

Mr S Pathak

Bristol Center for Surgical Research,

Population Health Sciences,

Canynge Hall

39 Whatley Road,

Bristol,

BS8 2PS.

Tel: +44 117 9287261

E-Mail: sp18580@bristol.ac.uk

Funding:

This study was supported by the MRC ConDuCT-II (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures) Hub for Trials Methodology Research (MR/K025643/1), and the NIHR Biomedical Research Center at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. JMB is an NIHR Senior Investigator and SP, BM and NSB are NIHR Clinical Lecturers.

Category: Systematic review

Conflict of Interest: nil

Word Count: 3077

Acknowledgements: The authors wish to thank Ms Catherine Borwick for her help in designing the search strategy

Key words:

Number of Tables: 5

Number of Figures: 1

Abstract

Introduction

The number of laparoscopic liver resections undertaken has increased. However, lesions located postero-superiorly are difficult to access. This may be overcome by the novel use of trans-thoracic port(s). Methods for the safe and transparent introduction of new and modified surgical procedures are limited and a summary of these issues, for minimally invasive trans thoracic liver resections (MITTLR), is lacking.

This study aims to understand and summarize technique description, governance procedures and reporting of outcomes for MITTLR.

Methods

A systematic literature search to identify primary studies of all designs describing MITTLR was undertaken. How patients were selected for the new technique was examined. The technical components of MITTLR were identified and summarized to understand technique development over time. Governance arrangements (e.g. IRB approval) and steps taken to mitigate harm were recorded. Finally, specific outcomes reported across studies were documented.

Results

Of 2067 83 screened articles, 16 were included reporting data from 145 patients and six countries. Selection criteria for patients was explicitly stated in two papers. No studies fully described the technique. Five papers reported ethical approval and three gave details of patient consent. No study reported on steps taken to mitigate harm.

Technical outcomes were commonly reported e.g. blood loss (15/16 studies), operative time (15/16) and margin status (11/16). Information on patient reported outcomes and costs were lacking.

Conclusions

Technical details and governance procedures were poorly described. Outcomes focussed on short term details alone. Transparency is needed for reporting the introduction of new surgical techniques to allow their safe dissemination.

Introduction

Liver resection for primary and secondary tumours is an effective oncological treatment and is increasingly being performed by laparoscopic techniques (1-3). Although systematic reviews suggest potential advantages of laparoscopic approaches (such as less blood loss and shorter hospital stay) compared to large abdominal wall incisions, the included studies were non-randomized (4-7). Recently, a single-center randomized controlled trial (RCT) compared open and laparoscopic surgery for patients undergoing parenchyma-sparing liver resection (8). This is the only reported RCT to compare the two techniques and although the study included over 200 patients, it was single center thus limiting generalizability. Despite the paucity of evidence, guidelines recommend that patients are considered for laparoscopic liver resections wherever possible (9).

Factors that can influence the decision to perform an operation laparoscopically include surgeon and multi-disciplinary team (MDT) expertise, center policy, infrastructure and approach to innovation (10, 11). Issues such as anatomy also need to be considered. Tumours situated posteriorly and superiorly within the liver are difficult to access using standard laparoscopic techniques because of the surrounding rib cage and diaphragm (12). In these circumstances, many surgeons undertake open surgery with an upper abdominal incision. To overcome these challenges, modifications to current minimally invasive techniques have been described. These modifications, known as minimally invasive trans-thoracic liver resection (MITTLR), involve placing intercostal transthoracic ports to improve access to the dome of the liver, in addition to

the laparoscopic abdominal ports. A totally trans-thoracic approach is where all the ports are placed through the diaphragm or pleura. The technique was first described in 2003 (13).

Currently, MITTLR is not in widespread use although early studies often suggest that a the technique is promising (14). It is well recognised that patients offered new techniques are highly selected (15). In addition, surgeons may under-report adverse events and are overly optimistic about innovation (16). The complexity of surgery (e.g. surgeon and team expertise, variations in pre- and post-operative management and variations in outcome reporting) poses challenges for rigorously evaluating new procedures (11).

Historically, surgical innovations have often been adopted without adequate evidence of efficacy or safety. Without proper evaluation, unevidenced based innovations have the potential to harm patients. Therefore, the Idea, Development, Exploration, Assessment, and Long-term Follow up (IDEAL) framework and recommendations were developed to facilitate evaluation of the introduction of complex interventional procedures (17, 18). However, there remain concerns around the processes of patient selection, information provision to patients, technique description (specifically, modifications and their rationale), governance procedures (including steps taken to mitigate against harms) and the selection of appropriate outcomes(19, 20). In view of these issues, it is hypothesised that a systematic review of the literature of an innovative technique and detailed analysis of reporting of study design and conduct would be valuable to understand current methods for surgical innovation and identify areas where further research and improvement is needed. To our knowledge, there has not been a previous systematic review of MITTLR, and no previous study has assessed the introduction of this new procedure into clinical practice. The aim of this study is therefore to report how MITTLR has been introduced

into clinical practice by summarizing technique description, governance procedures and how outcomes for MITTLR have been reported.

Methods

The methods are based on a published protocol for the analysis of innovative invasive procedures (21) and the review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) guidelines (22).

Inclusion criteria

All primary research study designs (e.g. case reports, case series, comparative series) describing 'transthoracic' or 'transdiaphragmatic' minimally invasive liver resections for benign or malignant conditions in adults or children were eligible for inclusion. Although review articles were not included *per se,* where identified the included studies were cross-referenced to ensure all sources of evidence were accessed. Pre-clinical and cadaveric studies were excluded as were editorial/expert opinion articles (23). ~~Non-English language papers,~~ Presentations and conference abstracts were excluded. Studies reporting outcomes on patients undergoing purely laparoscopic (without a trans-thoracic component) resections of postero-superior liver segments were excluded as were all duplicate studies.

Search strategy and study selection

Searches were undertaken in Medline, Embase, ~~CINAHL (Cumulative Index to Nursing and Allied Health Literature),~~ PubMed, Web of Science, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and Google Scholar, from inception until the 1st

April 2018. Search terms for trans-thoracic liver resection were combined using the Boolean 'AND' operator (see Appendix 1). Bibliographies of relevant studies and the "related articles" link in PubMed were used to identify additional studies. Search results were imported into EndNote© reference management software and de-duplicated.

Data extraction and management

A customised inclusion/exclusion proforma was developed to screen titles and abstracts. Screening was performed independently by at least two of four authors (SP, BGM, NSB, HFR). Differences between the authors were resolved by consensus with the study group. When no abstract was available, or the details were inadequate to enable a decision about eligibility, the full article was reviewed. The full-text versions of papers included after abstract screening were accessed for further assessment of their eligibility. Reference lists were manually searched for additional relevant articles. Data extraction was undertaken independently by at least two authors (SP, BGM, NSB, HFR) using a standardized proforma, and any disagreement resolved by consensus and/or discussion with the senior author (JMB). The following categories of data were extracted from included papers:

Characteristics of included studies

The type of study design, year and journal of publication, country of origin and number of participating centers and patients were recorded. If studies reported patient selection criteria these were documented to provide clarity about patients not suitable for the technique (to

prevent harm to future patients). Funding details or other potential conflicts of interest were documented.

Technique description and co-interventions:

The surgical description of the MITTLR technique reported was assessed using a typology which allows systematic deconstruction of an intervention to understand the individual surgical components and steps (24). This was undertaken because existing guidance (SPIRIT and TIDierR) for intervention description in study protocols does not request sufficient detail to understand how to reproduce a surgical procedure (25, 26). MITTLR was deconstructed according to its component parts (pre skin incision considerations, incision and access, dissection, resection, haemostasis, reconstruction, after skin closure and use of adjuncts). Then each paper was studied to understand which components had been reported. We also examined the authors' given rationale for changing components or adding or removing them based on their experience. This was done for each article chronologically. It allowed us to understand how the technique was undertaken and how it evolved over time

Co-interventions were documented. They were defined as interventions that naturally accompany or are associated with the intervention itself and can occur before, during or afterwards (27). For example, one lung ventilation using a dual lumen endo-tracheal tube may be considered a co-intervention during MITTLR.

Analysis of studies against IDEAL recommendations

Studies were retrospectively classified into IDEAL stages (17). Each study was then assessed to determine whether stage-specific IDEAL guidelines had been followed.

Surgeon expertise:

Details of the type of center undertaking the intervention, including previous case volumes any workload data were recorded. The number and level of seniority of surgeon(s), including their experience with minimally invasive liver surgery and MITTLR, were extracted. Documentation of whether any surgical learning curves were described was also recorded.

Governance arrangements:

Reporting of information describing governance approvals (ethics committee, hospital clinical governance departments, Institutional Review Board [IRB], clinical effectiveness committee and National Institute for Health and Care Excellence [NICE]) was documented because of the importance of transparent introduction of innovation.

Details regarding whether patient consent for the novel technique was obtained was recorded, specifically examining if patients were informed about the innovative nature of MITTLR. If reported, the number of patients declining the intervention was recorded as a measure of patient acceptability. Details of any steps taken to mitigate harm were recorded (e.g. whether an independent oversight committee reviewed the new procedure and its outcomes).

Outcome reporting

Information related to outcome reporting was collected in the following categories: adverse events (unintended injury or complication resulting in prolonged hospital stay, disability at the

time of discharge or death) (28), clinical (e.g. operative time and histological margin status), process (e.g. length of stay), patient-reported (report of the status of the patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician) (29), and economic outcomes. It is expected that the types of outcomes reported in studies evaluating innovative procedures focus on safety and efficacy – and acceptability to surgeon and patient.

Data synthesis and statistical analysis

Results are summarized in a narrative synthesis. No meta-analysis was performed because the purpose of this review was to describe how MITTLR is reported in the surgical literature rather than to compare outcomes with either open or laparoscopic liver resections.

Results

Of 2067 articles, 23 were identified for further review and 16 full papers were included (Figure 1).

Characteristics of included studies

The sixteen studies were performed in six countries and included 145 adult patients. The first was reported by a Japanese group in 2003 (13). There were six case reports (30-35) and 10 non-comparative single center studies (Table 1). Two stated patient inclusion criteria (13, 36).

Eleven papers stated that there were no conflicts of interest. Eight papers declared financial conflicts of interest, although only three studies were funded. All three (37-39) were from educational grants.

Technique description and co-interventions:

The index paper was a Japanese series describing three cases where tumours were excised using a totally trans-thoracic approach (13). The index paper did not provide a full deconstruction of the technique, although some components were well described (patient and port positioning, use of intra-operative USS, method of liver transection and specimen extraction). The subsequent paper(40) did reference the index paper and provided further understanding of patient suitability, anaesthetic co-interventions, port type used, technical factors such as haemostasis and use of drains (Table 2). The next paper to reference the index paper was (46) the seventh report. One other paper (41) referenced the index paper but neither study provided further insight into technique evolution.

Nine studies cited other papers describing MITTLR but did not reference the index paper (30, 31, 35-38, 41-43). None of these subsequent papers described each component step in detail and minor technical modifications were not documented or justified. It was therefore not possible to determine how the technique had evolved with time or whether specific components had evolved (Table 2). An opportunity for incremental learning to build upon the initial single centre reports was lost.

Steps of the procedure that were well reported (and continued to be well reported as the procedure evolved) included laparoscopic/thoracoscopic stack settings, patient positioning, port

placements, use of intra-operative ultrasound, liver mobilisation (if required) and parenchymal transection. Although most studies described port placement, there were variations between studies and hence changes over time were difficult to describe. It was not possible to track sequential development of the procedure over time. Items that were poorly reported such as 'pre theatre considerations' and 'factors causing conversion to open surgery' continued to be poorly reported as the procedure evolved.

Analysis of studies against IDEAL recommendations

All the studies were single-centre retrospective case studies and were therefore classed as IDEAL stage 2a ("procedure under development, performed by a few innovators and early adopters on a small number of patients"). Whilst the first paper would ordinarily be categorised as a stage 1 IDEAL study (i.e. first in human), this paper itself references a 'non-indexed' description of the first case. No studies made a protocol available for review. Selection criteria and proportion of eligible patients selected should also be reported – no papers provided the proportion of eligible patients recruited. Whilst patient characteristics and short-term clinical outcomes were generally well reported, cases were not reported sequentially and iterative changes to the technique (common in IDEAL stage 2a) were not clearly described. Ethical approval was reported in five studies and informed consent was not adequately described in any study (Table 3). Learning curves and methods to mitigate harm (e.g. mentoring for first few cases) were also not described in any of the papers.

Surgeon expertise:

None of the papers disclosed the center-specific caseload for either minimally invasive liver surgery or MITTLR. Only one study (44) stated the number of surgeons performing MITTLR (single surgeon) and level of seniority of participating surgeon was only provided in one paper (38). Furthermore, no studies reported specific training regarding the use of MITTLR for participating surgeons, the expertise of the team supporting the surgeon or use of a "preceptorship" during introduction of MITTLR to their center.

Governance arrangements:

Only five studies (37, 38, 41, 44, 45)reported that they had sought and been given ethical approval. Two studies documented registration with an institutional review board or hospital clinical governance department (46, 47). Three studies documented informed patient consent (37, 38, 48) although specific details about whether patients were informed about the innovative nature of MITTLR, and its associated risks, were not provided. None of the remaining papers mentioned consent at all. None of the included studies reported the number of patients declining the intervention. No studies mentioned any steps taken to mitigate harm and whether independent oversight committees reviewed MITTLR and its outcomes.

Outcome reporting:

Outcome reporting is summarized in Table 4. Two studies (38, 44) provided an *a priori* definition of adverse events.

Fifteen studies detailed complications without a single mortality reported. In terms of clinical outcomes, most of the studies reported blood loss (15/16) and margin status (11/16) as surrogate markers of surgical quality. Only three studies (36, 38, 49)mentioned factors likely to cause a

failure of the minimally invasive trans-thoracic approach and conversion to an open approach. Reasons for conversion included bleeding, poor views and concern about tumour margins. Operative time (14/16) and length of stay (14/16) were used as descriptors of process in most of the studies. Follow up was described in four studies and ranged from 4-61 months. Clinical outcomes are summarised in Table 5.

Patient reported outcomes and cost effectiveness were not measured in any of the studies.

Three studies drew no conclusion regarding MITTLR practice in the future, three studies felt further evaluation was warranted, seven studies felt the procedure was safe and feasible whilst three studies concluded that MITTLR should be adopted by surgeons.

Discussion

This is the first systematic review examining MITTLR. It identified 16 studies that were case reports and non-comparative case series. Whilst these small studies showed promising results the reporting limits their value to inform practice. Full technical description of the technique was lacking from all publications including the index study published in 2003 (13). Limited data on patient selection criteria and technique description were available. This means that it is challenging for other surgeons (early adopters) to reproduce the technique safely in appropriate patients. Errors may be inadvertently repeated. In addition, the governance arrangements (including patient consent) and regulatory approvals were poorly reported. Overall, current reporting of this innovative and evolving technique was poor and lacks rigor. Better and more transparent methods for evaluating and reporting new procedures are needed so that surgeons

adopting the technique can do so ethically and with minimal risk to patients, to optimise safe uptake.

Surgery is a complex intervention making it difficult to evaluate rigorously. The Idea, Development, Exploration, Assessment and Long-term Follow-up (IDEAL) framework, developed in 2009, is one proposed method for introducing and evaluating new surgical techniques (18). None of the reports describing MITTLR adhered to all the IDEAL guidelines, despite 15 of the 16 studies being published after IDEAL guidance became available. All the included studies would retrospectively be categorised as IDEAL stage 2a (development stage), suggesting that the technique has not yet stabilised, despite having been first reported over 15 years ago. There has been a lack of incremental learning and stepwise progression over the 15-year period – all 16 studies were either case reports or non-comparative single-centre, single-surgeon series. An opportunity to build upon this work and perform multi-centre studies with short- and long-term outcomes to provide insight into the technique has been missed. Learning curves could have been shortened by collaboration between the 'pioneering' surgeons to standardise techniques and outcomes to be monitored in future studies. This concept has been demonstrated in laparoscopic liver surgery where 'early adopters' who received specific training with standardisation of techniques had a shorter learning curve than the 'pioneering' surgeons (50). The non-adherence to IDEAL in evaluating MITTLR has may have resulted in reduced compliance with governance arrangements (gaining ethical approval and informed consent from patients) and poor study design with inadequate reporting of patient selection and technical modifications.

In this review, it was identified that most studies did not report that ethical (IRB) approval was obtained. The lack of formal ethical approval may be because surgeons view MITTLR as a simple

variation of laparoscopic surgery and therefore consider ethical approval unnecessary. A new or modified technique, however, could be associated with additional or unknown risks and provision of patients with such information is of importance. There may also be requirements to inform patients if a surgeon is undertaking a new procedure for the first time or if the technique is still evolving as the short and long-term sequalae may not yet be fully defined (51, 52). In addition to not reporting whether patient consent for a new procedure was obtained, it was noted that publications did not report the impact of the surgical learning curve on outcomes and whether steps were taken to mitigate potential harm to the patient as a surgeons' experienced developed. Methods to mitigate the effects of the learning curve include cadaveric training, visiting specialist centers and/or mentoring by visiting surgeons with expertise (53). No publications clearly reported how the surgeon's own experience and learning curve was relayed to patients.

Whilst this study is the largest and most comprehensive review of the literature reporting MITTLR to date, it has some limitations. Data from the papers were extracted verbatim and it was assumed that if information was not documented it did not happen. In addition, it was not possible to contact all authors individually to obtain further information about technique evolution and local governance arrangements. It is possible that early adopters may have implemented MITTLR in their clinical practise but have not yet published their results. Only full-text publications were included as it was considered that only these would provide the necessary methodological details required to robustly assess technique development, governance procedures and outcome reporting.

This study demonstrates significant deficiencies in the introduction of this innovative procedure with regards to i) description of patient selection, ii) information provision to patients, iii) technique description and iv) governance procedures. Surgical innovators should continue to use the IDEAL framework, although descriptions of patient selection, surgical technique, governance procedures and outcome reporting need to be optimised to ensure new procedures are reproducible.

To enhance the evaluation and adoption of novel procedures, there is a need to i) identify possible benefits early (and equally importantly, identify unsuccessful or harmful procedures so that they can be stopped in a timely way); ii) provide good leadership to champion and advocate adoption whilst encouraging continuous assessment of outcomes; iii) provide accurate descriptions of the technique and careful documentation of when (and why) this evolves; and iv) consider how impact will be measured. Information provision to patients detailing the innovative nature of the procedure, the surgeon's experience with the proposed procedure, the risks and benefits including uncertainty around risks and alternative treatments, are all crucial (54) .

Surgical innovation is required to develop novel procedures that improve patient outcomes. However, innovation it is important that this is conducted safely and transparently to optimise learning and minimise patient harm. Clear guidance and regulatory frameworks that build on IDEAL for surgical innovation are necessary.

References

1. Ardito F, Tayar C, Laurent A, Karoui M, Loriau J, Cherqui D. Laparoscopic liver resection for benign disease. Archives of surgery (Chicago, Ill : 1960). 2007;142(12):1188-93; discussion 93.
2. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg. 2009;250(5):831-41.
3. Belli G, Limongelli P, Fantini C, D'Agostino A, Cioffi L, Belli A, et al. Laparoscopic and open treatment of hepatocellular carcinoma in patients with cirrhosis. Br J Surg. 2009;96(9):1041-8.
4. Croome KP, Yamashita MH. Laparoscopic vs open hepatic resection for benign and malignant tumors: An updated meta-analysis. Archives of surgery (Chicago, Ill : 1960). 2010;145(11):1109-18.
5. Simillis C, Constantinides VA, Tekkis PP, Darzi A, Lovegrove R, Jiao L, et al. Laparoscopic versus open hepatic resections for benign and malignant neoplasms--a meta-analysis. Surgery. 2007;141(2):203-11.
6. Goh EL, Chidambaram S, Ma S. Laparoscopic vs open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: A meta-analysis of the long-term survival outcomes. International journal of surgery (London, England). 2018;50:35-42.
7. Rao AM, Ahmed I. Laparoscopic versus open liver resection for benign and malignant hepatic lesions in adults. The Cochrane database of systematic reviews. 2013(5):Cd010162.
8. Fretland AA, Dagenborg VJ, Bjornelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Ann Surg. 2018;267(2):199-207.
9. Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Ann Surg. 2017.
10. Marusch F, Gastinger I, Schneider C, Scheidbach H, Konradt J, Bruch HP, et al. Experience as a factor influencing the indications for laparoscopic colorectal surgery and the results. Surgical endoscopy. 2001;15(2):116-20.
11. Cook JA, McCulloch P, Blazeby JM, Beard DJ, Marinac-Dabic D, Sedrakyan A. IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage. BMJ (Clinical research ed). 2013;346:f2820.
12. Fuks D, Gayet B. Laparoscopic surgery of postero-lateral segments: a comparison between transthoracic and abdominal approach. Updates in Surgery.67(2):141-5.
13. Teramoto K, Kawamura T, Takamatsu S, Noguchi N, Nakamura N, Arii S. Laparoscopic and thoracoscopic partial hepatectomy for hepatocellular carcinoma. World J Surg. 2003;27(10):1131-6.
14. Agha RA, Fowler AJ, Rajmohan S, Barai I, Orgill DP. Preferred reporting of case series in surgery; the PROCESS guidelines. International journal of surgery (London, England). 2016;36(Pt A):319-23.
15. Abad C, Caceres JJ, Alonso A. Fatal pulmonary thromboembolism after laparoscopic cholecystectomy. Surgical Endoscopy.15(11):1360.
16. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017;18(1):122.
17. McCulloch P, Feinberg J, Philippou Y, Kolias A, Kehoe S, Lancaster G, et al. Progress in clinical research in surgery and IDEAL. Lancet (London, England). 2018;392(10141):88-94.
18. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet (London, England). 2009;374(9695):1105-12.
19. Currie A, Brigic A, Blencowe NS, Potter S, Faiz OD, Kennedy RH, et al. Systematic review of surgical innovation reporting in laparoendoscopic colonic polyp resection. The British journal of surgery. 2015;102(2):e108-16.

20. Muskens IS, Diederen SJH, Senders JT, Zamanipoor Najafabadi AH, van Furth WR, May AM, et al. Innovation in neurosurgery: less than IDEAL? A systematic review. Acta Neurochir (Wien). 2017;159(10):1957-66.
21. Main BG, Blencowe NS, Howes N, Cousins S, Avery KNL, Gormley A, et al. Protocol for the systematic review of the reporting of transoral robotic surgery. BMJ Open. 2018;8(1):e019198.
22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.
23. Gotzsche PC, Ioannidis JP. Content area experts as authors: helpful or harmful for systematic reviews and meta-analyses? BMJ (Clinical research ed). 2012;345:e7031.
24. Blencowe NS, Mills N, Cook JA, Donovan JL, Rogers CA, Whiting P, et al. Standardizing and monitoring the delivery of surgical interventions in randomized clinical trials. The British journal of surgery. 2016;103(10):1377-84.
25. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ (Clinical research ed). 2013;346:e7586.
26. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ (Clinical research ed). 2014;348:g1687.
27. Blencowe NS, Brown JM, Cook JA, Metcalfe C, Morton DG, Nicholl J, et al. Interventions in randomised controlled trials in surgery: issues to consider during trial design. Trials. 2015;16:392.
28. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Quality & safety in health care. 2008;17(3):216-23.
29. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). Health services insights. 2013;6:61-8.
30. Kruger JA, Coelho FF, Perini MV, Herman P. Laparoscopic transthoracic liver resection. ABCD, Arquivos Brasileiros de Cirurgia Digestiva.27(4):288-90.
31. Hallet J, Soler L, Diana M, Mutter D, Baumert TF, Habersetzer F, et al. Trans-thoracic minimally invasive liver resection guided by augmented reality. Journal of the American College of Surgeons.220(5):e55-60.
32. Aikawa M, Miyazawa M, Okamoto K, Toshimitsu Y, Okada K, Ueno Y, et al. Thoracoscopic hepatectomy for malignant liver tumor. Surgical Endoscopy.28(1):314.
33. Schwarz L, Aloia TA, Eng C, Chang GJ, Vauthey JN, Conrad C. Transthoracic Port Placement Increases Safety of Total Laparoscopic Posterior Sectionectomy. Ann Surg Oncol. 2016;23(7):2167.
34. Yamashita S, Loyer E, Kang HC, Aloia TA, Chun YS, Mehran RJ, et al. Total Transthoracic Approach Facilitates Laparoscopic Hepatic Resection in Patients with Significant Prior Abdominal Surgery. Ann Surg Oncol. 2017;24(5):1376-7.
35. Jang JY, Han HS, Yoon YS, Cho JY, Choi Y, Lee W, et al. Three-Dimensional Laparoscopic Anatomical Segment 8 Liver Resection with Glissonian Approach. Ann Surg Oncol. 2017;24(6):1606-9.
36. Hirokawa F, Hayashi M, Asakuma M, Shimizu T, Inoue Y, Uchiyama K. Intercostal Trocars Enable Easier Laparoscopic Resection of Liver Tumors in Segments 7 and 8. World J Surg. 2017;41(5):1340-6.
37. Ichida H, Ishizawa T, Tanaka M, Terasawa M, Watanabe G, Takeda Y, et al. Use of intercostal trocars for laparoscopic resection of subphrenic hepatic tumors. Surgical Endoscopy.31(3):1280-6.
38. Inoue Y, Suzuki Y, Fujii K, Kawaguchi N, Ishii M, Masubuchi S, et al. Laparoscopic Liver Resection Using the Lateral Approach from Intercostal Ports in Segments VI, VII, and VIII. J Gastrointest Surg. 2017;21(12):2135-43.
39. Ishizawa T, Gumbs AA, Kokudo N, Gayet B. Laparoscopic segmentectomy of the liver: from segment I to VIII. Ann Surg. 2012;256(6):959-64.

40. Cloyd JM, Visser BC. Video-assisted thoracoscopic transdiaphragmatic liver resection for hepatocellular carcinoma. Surgical Endoscopy.26(6):1772-6.
41. Lee W, Han HS, Yoon YS, Cho JY, Choi Y, Shin HK. Role of intercostal trocars on laparoscopic liver resection for tumors in segments 7 and 8. Journal of hepato-biliary-pancreatic sciences. 2014;21(8):E65-8.
42. Ogiso S, Conrad C, Araki K, Nomi T, Anil Z, Gayet B. Laparoscopic Transabdominal With Transdiaphragmatic Access Improves Resection of Difficult Posterosuperior Liver Lesions. Annals of Surgery.262(2):358-65.
43. Yamashita S, Loyer E, Kang HC, Aloia TA, Chun YS, Mehran RJ, et al. Total Transthoracic Approach Facilitates Laparoscopic Hepatic Resection in Patients with Significant Prior Abdominal Surgery. Annals of Surgical Oncology.24(5):1376-7.
44. Chiow AK, Lewin J, Manoharan B, Cavallucci D, Bryant R, O'Rourke N. Intercostal and transthoracic trocars enable easier laparoscopic resection of dome liver lesions. HPB.17(4):299-303.
45. Guro H, Cho JY, Han HS, Yoon YS, Choi Y, Jang JS, et al. Laparoscopic liver resection of hepatocellular carcinoma located in segments 7 or 8. Surg Endosc. 2018;32(2):872-8.
46. Guro H, Cho JY, Han HS, Yoon YS, Choi Y, Jang JS, et al. Laparoscopic liver resection of hepatocellular carcinoma located in segments 7 or 8. Surgical Endoscopy. 2018;32(2):872-8.
47. Lee W, Han HS, Yoon YS, Cho JY, Choi Y, Shin HK. Role of intercostal trocars on laparoscopic liver resection for tumors in segments 7 and 8. Journal of Hepato-biliary-pancreatic Sciences. 2014;21(8):E65-8.
48. Aikawa M, Miyazawa M, Okamoto K, Toshimitsu Y, Okada K, Ueno Y, et al. Thoracoscopic hepatectomy for malignant liver tumor. Surg Endosc. 2014;28(1):314.
49. Ichida H, Ishizawa T, Tanaka M, Terasawa M, Watanabe G, Takeda Y, et al. Use of intercostal trocars for laparoscopic resection of subphrenic hepatic tumors. Surg Endosc. 2017;31(3):1280-6.
50. Halls MC, Alseidi A, Berardi G, Cipriani F, Van der Poel M, Davila D, et al. A Comparison of the Learning Curves of Laparoscopic Liver Surgeons in Differing Stages of the IDEAL Paradigm of Surgical Innovation: Standing on the Shoulders of Pioneers. Ann Surg. 2019;269(2):221-8.
51. Rogers WA, Hutchison K, McNair A. Ethical Issues Across the IDEAL Stages of Surgical Innovation. Ann Surg. 2019;269(2):229-33.
52. Johnson J, Rogers W, Lotz M, Townley C, Meyerson D, Tomossy G. Ethical challenges of innovative surgery: a response to the IDEAL recommendations. Lancet. 2010;376(9746):1113-5.
53. Broekman ML, Carriere ME, Bredenoord AL. Surgical innovation: the ethical agenda: A systematic review. Medicine (Baltimore). 2016;95(25):e3790.
54. England R. Surgical Innovation, New Techniques and Technologies 2019 [Available from: https://www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/surgical-innovation/.

Figure 1: PRISMA Flowchart depicting the search strategy and selection of articles for the review

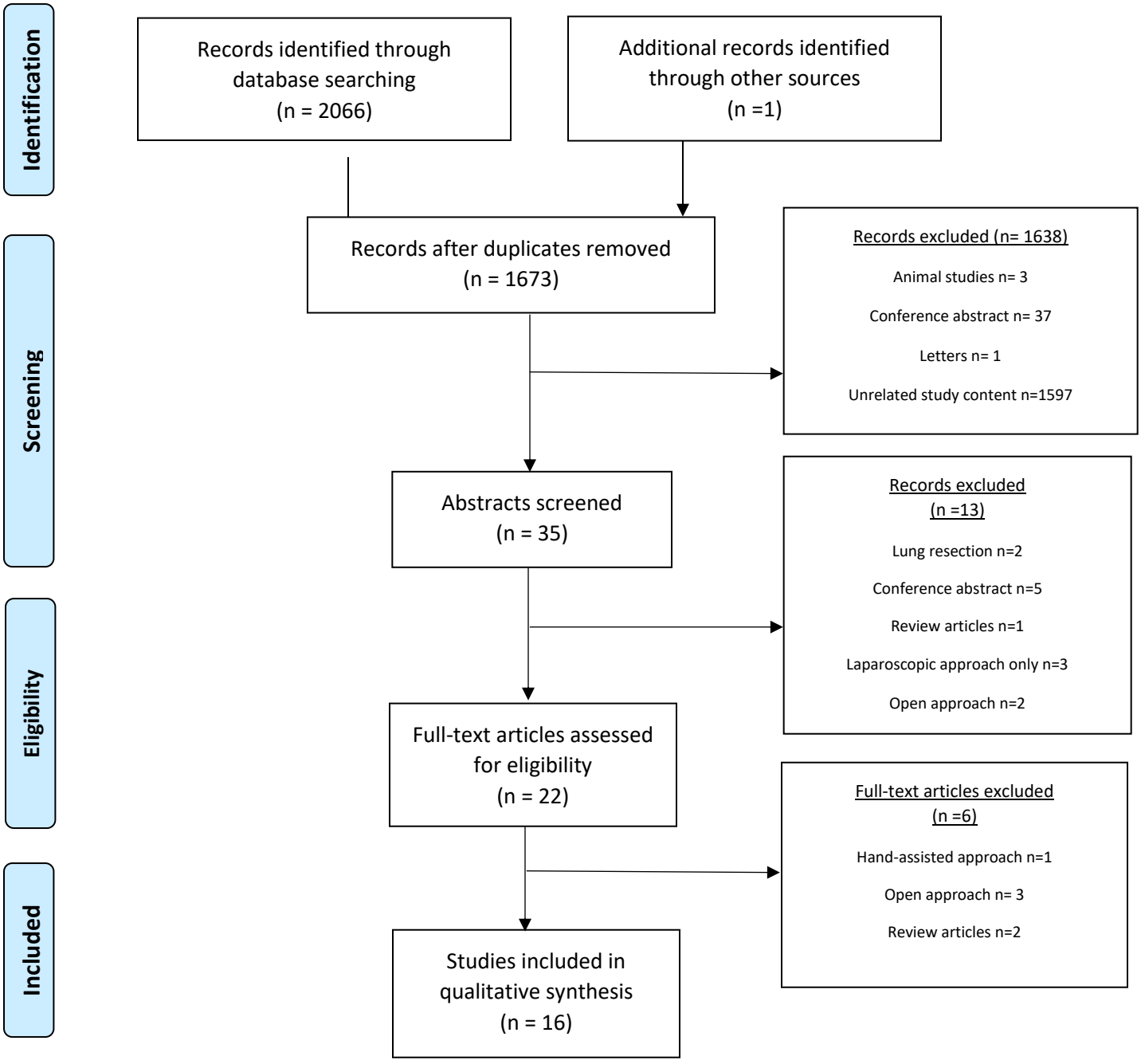


Table 1; Characteristics of included studies

Paper number	Author	Journal	Year of publication	Country	Type of study	~~Patients (N)~~
1	Teramoto (13)	World Journal of Surgery	2003	Japan	NCS	~~3~~
2	Cloyd (40)	Surgical Endoscopy	2012	USA	NCS	~~2~~
3	Ishizawa (39)	Annals of Surgery	2012	France	NCS	~~10~~
4	Aikawa (48)	Surgical Endoscopy	2014	Japan	V/CR	~~1~~
5	Kruger (30)	Arquivos Brasileiros de Cirurgia Digestiva	2014	Brazil	CR	~~1~~
6	Lee (41)	Journal of HBP Sciences	2014	South Korea	CS	~~5~~
7	Chiow (44)	HPB Journal	2015	Australia	RC	~~8~~
8	Hallet (31)	Journal of American College of Surgeons	2015	France	CR	~~1~~
9	Ogiso (42)	Annals of Surgery	2015	France	RC	~~25~~
10	Schwarz (33)	Annals of Surgical Oncology	2016	USA	V/CR	~~1~~
11	Yamashita (34)	Annals of Surgical Oncology	2017	USA	V/CR	~~1~~
12	Ichida (37)	Surgical Endoscopy	2017	Japan	NCS	~~14~~
13	Hirokawa (36)	World Journal of Surgery	2017	Japan	RC	~~23~~
14	Inoue (38)	J Gastrointestinal Surg	2017	Japan	RC	~~32~~
15	Jang (35)	Annals of Surgical Oncology	2017	South Korea	CR	~~1~~

16	Guro (45)	Surgical Endoscopy	2018	South Korea	RC	~~17~~

** NCS- non-comparative study

V- video presentation

CR- Case report

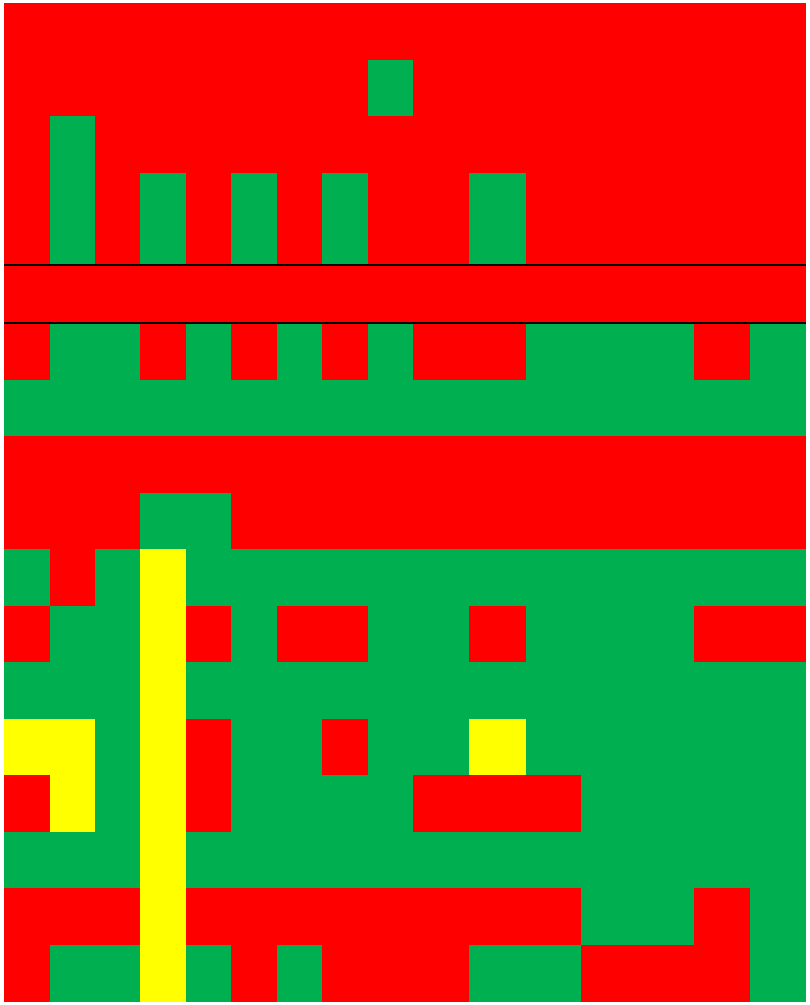
CS- Case series

RC- Retrospective Cohort

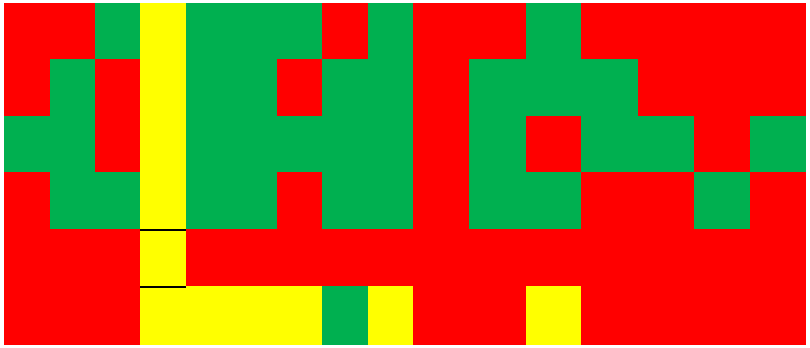
HPB- Hepato-pancreato-biliary

Table 2: Description of component parts of MITTLR by study

Component		Paper number
		1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Pre-theater considerations	MDT discussion	
	Radiological criteria for selection	
	Patient suitability	
Pre-incision anaesthetic considerations	Dual v single lumen ET tube	
Pre-incision surgical considerations	Stack set up	
	Stack settings	
	Patient positioning	
	Skin preparation	
Incision and access	Induction of pneumoperitoneum	
	Port placement	
	Port types	
Dissection	Intra-operative USS	
	Liver mobilisation (if needed)	
	Inflow control (if needed)	
Resection	Liver parenchyma transection	
	Factors causing conversion to open surgery	
Haemostasis		



Insertion of surgical adjuncts	Insertion of abdominal drain
	Insertion of chest drain
Closure	Specimen extraction
	Closure of diaphragm
After skin closure	Post-operative CXR
	Removal of chest drain



	Yes
	No
	N/A

NA applies if a) chest drain not inserted in first place, b) liver mobilisation not possible (trans-thoracic only) c) one paper was a video which was incomplete

Table 3: Analysis of studies against IDEAL recommendations

	Paper															
Stage 2a recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Make protocol for study available	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Use standard, well-defined measures for reporting outcome and patient characteristics	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Report and explain all exclusions	Y	N/a	N	N/a	N/a	Y	Y	N/a	Y	N/a	N/a	Y	Y	Y	N/a	Y
Report all cases sequentially with annotation and explanation of changes to indication of procedure and when and why they took place	N	N/a	N	N/a	N/a	N	N	N/a	N	N/a	N/a	N	N	N	N/a	N
Display main outcome graphically showing cases sequentially to illustrate when changes took place	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Informed consent should explain status of innovation and consequent uncertainties around risk	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Key:

Y = yes, N = no

*N/A (as study was a case report)

Table 4: Reporting of approval, governance and outcomes in MITTLR studies

	Number of Studies n=16 (%)
Ethics approval obtained	5 (31)
Source of funding declaration	8 (50)
Conflict of interest	11 (68.5)
Patient consent obtained	3 (18.8)
Information about innovative nature of procedure explained to patients	0 (0)

Adverse events	15 (94)
Clinical outcomes	16 (100)
Process outcomes	16 (100)

Table 5: A summary of Clinical Outcomes

Author	Patients (N)	Operating time (minutes)	Blood loss (ml)	Transfusions	Conversions	Size of tumour (mm)	Indication	Surgical margin (mm)	Length of stay (days)	Complications	Observation period (months)
Teramoto (13)	3	198-310	50-650	NR	NR	17/20 – 14/47	HCC	2-5mm	8-18	0	13-61
Cloyd (40)	2	NR	NR	NR	NR	23/22– 20/20	HCC	negative	3-5	0	7-12
Ishizawa (39)	10	180-240	100-1200	1	1	NR	NR	NR	NR	2 (not specified)	NR
Aikawa (48)	1	310	10	0	0	NR	CRLM	NR	4	0	NR
Kruger (30)	1	75	20	NR	NR	20	HCC	NR	2	0	4
Lee (41)	5	197 (mean)	161 (mean)	0	NR	22 (mean)	CRLM (3), Breast Ca metastases (1), HCC (1)	5.8 (mean)	7 (mean)	0	12.4 (mean)

Chiow (44)	8	50-150	50-300	NR	0	6-34	CRLM (5), other (3)	1-11	1-4	0	NR
Hallet (31)	1	270	300	0	0	40	HCC	NR	4	0	NR
Ogiso (42)	25	90-390	20-2900	1	0	8-49	CRLM (18), other metastases (6), HCC (1)	0-13	4-22	biliary fistula (1), diaphragmatic hernia (1)	NR
Schwarz (33)	1	300	100	NR	NR	24	CRLM	30	4	0	NR
Yamashita (34)	1	247	100	0	0	necrosed	CRLM	5	NR	0	NR
Ichida (37)	14	109-477	20-310	NR	1	6-25	Liver mets (11), HCC (2), hemangioma (1)	1-20	6-19	0	NR
Hirokawa (36)	23	130-427	10-480	NR	1	15-60	HCC (9) Other (13)	3-12	6-15	Wound infection (1), pleural effusion (1)	NR
Inoue (38)	32	119-427	0-150	4	1	9-60	HCC/ICC (13), metastases/others (19)	0-16	6-22	Clavien-Dindo classification >IIIA (1),	NR
Jang (35)	1	420	600	0	0	66	HCC	3	6	0	NR
Guro (45)	17	NR	500	NR	NR	NR	NR	NR	7	NR	NR

Appendix 1; Search Strategy

For Ovid Medline (1946-):

1 Hepatectomy/ae, co, is, mt [Adverse Effects, Complications, Instrumentation, Methods]
2 Thoracoscopy/ae, co, is, mt [Adverse Effects, Complications, Instrumentation, Methods]
3 Thoracic Surgery, Video-Assisted/ae, is, mt [Adverse Effects, Instrumentation, Methods]
4 hepatectom*.ti,ab,kf.
5 ((surgery or surgical or thoracic or thorascop*) adj3 liver).ti,ab,kf.
6 1 or 2 or 3 or 4 or 5
7 (transthoracic or trans-thoracic).ti,ab,kf.
8 (transdiaphragmatic or trans-diaphragmatic).ti,ab,kf.
9 (intercostal or inter-costal).ti,ab,kf.

10 7 or 8 or 9
11 6 and 10

For Ovid Embase (1974-):

1 exp liver resection/
2 thoracoscopy/
3 laparoscopy/
4 video assisted thoracoscopic surgery/
5 hepatectom*.ti,ab,kw.
6 ((surgery or surgical or thoracic or thoracoscop*) adj3 liver).ti,ab,kw.
7 (transdiaphragmatic or trans-diaphragmatic).ti,ab,kw.
8 (transthoracic or trans-thoracic).ti,ab,kw.
9 (intercostal or inter-costal).ti,ab,kw.
10 1 or 2 or 3 or 4 or 5 or 6
11 7 or 8 or 9
12 10 and 11

For Web of science:

1 ((liver or hepatic) SAME (resection* or segmentectomy or surgery or surgical or thoracic or thorascop*))
2 Hepatectom*
3 1 or 2
4 (trans$thoracic or trans$diaphragmatic or inter$costal)
5 3 and 4

For Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 7)) in *The Cochrane Library*

1 MeSH descriptor: Hepatectomy/ae, co, is, mt [Adverse Effects, Complications, Instrumentation, Methods]
2 hepatectom*
3 ((surgery or surgical or thoracic or thorascop* or laporascop*) NEAR (hepatic or liver)

6 1 or 2 or 3

7 (transthoracic or trans-thoracic)

8 (transdiaphragmatic or trans-diaphragmatic)

9 (intercostal or inter-costal)

10 7 or 8 or 9

10 6 and 10